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Original Article

Intermittent hypoxemia and sleep fragmentation: associations with daytime alertness in obese sleep apnea patients living at moderate altitude

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ABSTRACT

Background: Although obstructive sleep apnea (OSA) has long been associated with daytime sleepiness, far less is known about its association with the ability to remain awake. The aim of this study was to examine the relative importance of inter-correlated measures of OSA severity (eg, various indices of oxygen saturation and sleep fragmentation) in the ability to stay alert as measured objectively by the Maintenance of Wakefulness Test (MWT), defined by a mean sleep latency of ≥12 min.
Methods: Seventy-eight obese women and men of similar age and body mass index living at altitude (Mexico City) underwent standard polysomnography, MWT, and completed validated sleep-related questionnaires.
Results: Men had more severe sleep apnea than women ($p = 0.002$) and were also less alert on MWT ($p = 0.022$). Logistic regression models indicated that measures of desaturation consistently predicted MWT-defined alertness, whereas varied measures of sleep fragmentation did not. Nearly a third of the variance ($r^2 = 0.304$) in MWT-defined alertness was accounted for by the number of desaturations per hour of sleep ($p = 0.003$), which is considerably higher than other studies have reported in different populations.
Conclusion: The ability to remain awake in obese patients is best accounted for by hypoxemia rather than sleep fragmentation. Whether the size of this effect reflects differences in the population under study (eg, extent of obesity, racial background, residence at moderate altitude) and/or is a function of the measurement of alertness with the MWT remains uncertain.

1. Introduction

Since the initial clinical descriptions of OSA [1], hypersomnolence has been one of the main hallmarks of this syndrome. However, not all patients with OSA have hypersomnolence. In fact, in the Sleep Heart Health Study, approximately more than half of individuals with severe OSA did not have subjective hypersomnolence as measured by the Epworth Sleepiness Scale (ESS) [2,3]. In addition, there may be sex differences in the association between OSA and subjective or objective measures of sleepiness, with men demonstrating higher levels of hypersomnolence than women [4,5].

It remains unclear why some individuals with OSA show sleepiness and others do not. Some studies have found an association between measures of intermittent hypoxemia and sleepiness measured with the Multiple Sleep Latency Test (MSLT) [6–9], whereas

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a fewer number have measured alertness with the Maintenance of Wakefulness Test (MWT) [10–12], a procedure that is often considered to have more face validity than the MSLT. Some of these studies report that measures of nocturnal hypoxemia account for the most variance in daytime measures [6,7], whereas others indicated that measures of sleep fragmentation were more strongly associated with such variables [9,13]. Regardless of whether MSLT or MWT has been used, studies attempting to account for the daytime sleepiness or alertness of the OSA patient have successfully predicted only small amounts of variance with measures derived from polysomnography, typically of the order of 10–15% or less [10–12]. The reasons why polysomnographically derived variables have a low predictive value have long remained a matter of debate.

The primary objective of the current study was to examine the factors associated with the ability to maintain wakefulness in a cohort of obese men and women living at moderate altitude in Mexico City referred to a sleep disorders clinic. The secondary objective was to evaluate whether sex differences had differential impact on those associations.

2. Methods

Our study included both women and men of similar age and body mass index (BMI) and compared the clinical symptoms and polysomnographic features between genders. We prospectively approached all consecutive patients referred to the sleep clinic of the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán (INCMNSZ), which is a tertiary healthcare center in México City (2240 m above sea level), serving the local population. Almost all patients referred to our sleep clinic for suspicion of sleep-disordered breathing are obese, and given limited resources for the research, this population was the focus of our work.

This study was conducted in accordance with the amended Declaration of Helsinki and was approved by the INCMNSZ Institutional Committee for Biomedical Research Involving Humans (protocol # 1387); written informed consent was obtained from all patients. To be included in the study, patients had to have a BMI ≥ 30 kg/m^2 and had to provide written informed consent ($N = 128$); in addition, they must not have had a history of hypothyroidism, hypoventilation, chronic obstructive pulmonary disease, heart failure, major psychiatric and neurological disorders, current use of psychotropics or hypnotics, they must not have been shift workers, or have been treated with positive pressure or have undergone bariatric surgery. Our final analytic cohort included 78 obese participants (55 men and 23 women).

Patients spent two consecutive nights in the sleep laboratory to undergo two nights of polysomnography (PSG), and after the second night, each underwent an MWT. Questionnaires for depression, sleep habits, and sleep symptoms were administered prior to the first night PSG. The Epworth Sleepiness Scale (ESS) was administered on the same day as the MWT. Waist and hip circumferences were taken to derive waist-to-hip ratio. Neck circumference measurements were made at the most prominent portion of the thyroid cartilage [14,15]. Blood pressure measurements were performed at the time of the initial PSG using standard techniques with an appropriate cuff size for obesity. Arterial hypertension was defined as either systolic blood pressure of 140 mmHg or higher, diastolic blood pressure of 90 mmHg or higher, or current use of antihypertensive drugs. We used the Beck Depression Inventory–II [16] (BDI) adapted for and validated in a Mexican population by Jurado-Cárdenas et al. [17], and Gonzáles et al. [18] which has been shown to have an internal consistency of Cronbach's alpha = 0.78 [17] and alpha = 0.87 [18]. Normative values for Mexican population are as follows: minimal 0–13; mild depression 14–19; moderate depression 20–28; severe depression 29–63.

The Sleep Habits Questionnaire collected data on demographics, sleep habits (hours of sleep, time of sleep, etc.), napping behavior, drinking behavior, and smoking habits. This questionnaire has been described previously [19]. The ESS was completed on the day of MWT prior to the first nap. The ESS has been shown to be a reliable self-reported instrument to measure sleepiness [20,21]. We previously validated the ESS against the MSLT and the MWT in the native Mexican population [22].

2.1. Study design and PSG

All the recordings were generated on a Nicvue system (version 2.6, 2004, Viasys Healthcare, Inc, St Louis, MO, USA) and consisted of simultaneous monitoring of surface electroencephalogram, electrooculogram, surface mentalis and bilateral anterior tibialis electromyograms, and the electrocardiogram (ECG) (Lead II). Respiratory movements were monitored using plethysmography bands. Oral/nasal airflow was monitored with a four-bead thermistor system and a pressure transducer airflow sensor. Oxygen saturation (SpO_2) was recorded with an ear pulse oximeter (BCI-9000, BCI, Inc., Waukesha, WI, USA). Recordings began at the typical bedtimes of the subjects and ended at their typical wake up time in the morning. We recorded two consecutive nights of PSG and used night 2 in order to minimize the first-night effect. Quantitative evaluations of sleep stages were generated visually by an experienced technologist using the American Academy of Sleep Medicine (AASM) rules [23]. The number of abnormal breathing events per hour of sleep was quantified as the apnea–hypopnea index or AHI (the sum of apneas and hypopneas per hour of sleep). Obstructive apneas were scored with a drop in the peak signal excursion by ≥90% of pre-event baseline using the oronasal thermal sensor for a duration ≥ 10 s associated with continued inspiratory effort. Central apneas were scored if the apnea criteria were met but with absent inspiratory effort throughout the entire period of absent airflow [23]. Mixed apneas were scored if the apnea criteria were met and it was associated with concomitant absent inspiratory effort in the initial portion of the event, followed by resumption of inspiratory effort in the second portion of the event. Hypopneas were scored if the nasal pressure excursion signal dropped by ≥30% of baseline for a minimum duration of at least 10 s accompanied by a ≥4% drop in oxygen saturation (SpO_2) from the pre-event baseline. We defined the presence of sleep apnea as AHI ≥ 5 events per hour. The oxygen desaturation index (ODI) was defined as the number of drops in $SpO_2 \geq 4\%$ per hour of sleep. Periodic limb movements (PLM) were scored based on AASM rules [23] and were quantified as the number of leg movements per hour to yield a PLM Index (PLMI).

An arousal was scored according to AASM guidelines if there was an abrupt shift of EEG frequency including alpha, theta, and/or frequencies greater than 16 Hz lasting at least 3 s, with at least 10 s of stable sleep preceding the change. Scoring of arousal during REM sleep required a concurrent increase in submental EMG lasting at least 1 s. Arousal index was calculated based on number of arousal × 60/TST and they were subclassified into those associated with respiratory events, those associated with leg movements, and those not associated with either a respiratory event or leg movement.

2.2. MWT

The MWT derives from the premise that volitional ability provides important information regarding the ability to stay awake [24,25]. Studies have demonstrated significant differences in the mean sleep latencies between normal healthy subjects and patients with hypersomnia with this test, and it is more sensitive to treatment effects than the MSLT. We have previously documented in obese subjects who underwent bariatric surgery, that even though there is a noticeable decrease in body weight after one year of